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No effect of an additional early dose of measles vaccine on hospitalization or mortality in children: A randomized controlled trial

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ABSTRACT

Background: Non-specific effects (NSEs) of vaccines have increasingly gained attention in recent years. Recent studies suggest that live vaccines, such as measles vaccine (MV), have beneficial effects on health, while inactivated vaccines, such as the diphtheria-tetanus-pertussis (DTP) vaccine, may have harmful effects. If this is the case, it should improve child health to move MV closer to the last vaccination with DTP. The objective of this study was to investigate the NSEs of an additional early dose of MV on hospitalization or mortality.

Methods: Children were randomized to receive either the standard MV at 9 months (control) or an additional early dose of MV 4 weeks after the third dose of DTP-containing Pentavalent vaccine and the standard MV at 9 months (intervention). In this analysis of a secondary outcome in the trial, we investigated the effect of the intervention on a composite endpoint of over-night hospitalization with or without recovery, or death without previous hospitalization, in children between 4.5 and 36 months of age in the Nouna HDSS in Burkina Faso. We used Cox proportional hazards regression with repeated events and time since study enrolment as underlying time-scale.

Results: Among 2258 children in the intervention and 2238 children in the control group we observed a total of 464 episodes of hospitalization or mortality. There was no difference between intervention and control group (HR = 1.00, 95% Confidence Interval (CI) 0.83–1.20). Results from the per-protocol and intention-to-treat analysis were similar. Although no significant, results suggest a possible beneficial effect of early MV in children that had not been exposed to an OPV campaign after enrolment (HR = 0.83, 95% CI 0.55–1.29).

Conclusions: We did not detect any effect of early MV on subsequent hospitalization or mortality. However, possible effects of early MV could have been obscured by NSEs of the frequent OPV campaigns.

Conclusions: Registration: The trial was registered at ClinicalTrials.gov, NCT01644721

1. Background

Non-specific effects (NSEs) of vaccines have increasingly come into focus [1–4]. NSEs are harmful or beneficial health effects of vaccines which are unrelated to the target disease of the vaccine. If the vaccinated children show better health outcomes than unvaccinated children beyond what would be expected by prevention of the target disease, the vaccine is considered to have beneficial non-specific effects. Such effects have been shown for Bacillus Calmette-Guérin (BCG), the tuberculosis vaccine, for which meta-analyses of randomized controlled trials (RCTs) have reported a borderline-significant decrease of 30% in child mortality [2] and a highly significant 38% reduction in neonatal mortality among babies with low birth weight [4]. A similar borderline-significant decrease in child mortality of about 26% was shown for measles vaccine (MV) [2]. Very recently, non-specific beneficial effects have also been shown for oral polio vaccine (OPV) by one RCT and two

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observational studies from Guinea-Bissau [5–7]. Contrary to this, results from observational studies suggest the possibility that the inactivated trivalent vaccine to protect against diphtheria, tetanus, and pertussis (DTP) has non-specific harmful effects on child survival [2].

The main pattern behind these findings is that live vaccines (BCG, MV, and OPV) seem to have beneficial NSEs, while inactivated vaccines, such as DTP, seem to have harmful effects [1]. The theory is that live vaccines modify immune response also to unrelated pathogens and recent *in vitro* and *in vivo* immunological research supports this theory [3,8,9].

In countries with measles transmission, the World Health Organization (WHO) recommends the first dose of MV at 9 months and a second dose later in childhood to provide the best protection against measles [10]. This recommendation does not take NSEs of vaccinations into account. In Burkina Faso, the age of MV is four to five months after the last dose of DTP, which is given in three doses at 8, 12, and 16 weeks of age. If there are indeed harmful NSEs of DTP and beneficial effects of MV, it should improve child health to provide measles vaccination earlier in life and closer to the last vaccination with DTP because this would reduce exposure time to DTP, i.e. the time, when DTP is the most recent vaccine [11,12].

Apart from NSEs on child mortality, studies have recently started looking into less severe outcomes, such as hospitalization and mother-reported disease symptoms [13–15]. Results suggest that MV may have beneficial NSEs also on less severe outcomes. This is interesting not only for settings with high but also with low levels of child mortality because beneficial NSEs of MV could improve child health in a wider range of populations.

In this study, we investigated the NSEs of an additional early dose of MV at 4–7 months of age on a composite endpoint defined as over-night hospitalization or death without previous hospitalization, in a randomized controlled trial in rural Burkina Faso.

2. Methods

2.1. Study area

This study was conducted in the Nouna Health and Demographic Surveillance System (HDSS) in north-western Burkina Faso, which currently comprises a population of about 100,000 inhabitants. The population has been under continuous surveillance since 1993, with registration of births, deaths, migration, as well as a number of socio-demographic variables [16].

At the initiation of the trial, the routine vaccination program in Burkina Faso recommended five different vaccines: (i) BCG, (ii) OPV, (iii) Pentavalent Vaccine against DTP, hepatitis B, and *Haemophilus influenzae* type b (Penta), (iv) Yellow fever vaccine (YFV), and (v) MV. The recommended vaccination schedule in Burkina Faso is BCG and first dose of OPV (OPV0) at birth, first dose of Penta (Penta1) and OPV1 at 8 weeks, Penta2 and OPV2 at 12 weeks, Penta3 and OPV3 at 16 weeks, and MV combined with YFV at 9 months of age [17].

2.2. Objective and study design

The objective of the RCT was to investigate the NSEs of an additional dose of MV, given 4 weeks after Penta3, on child mortality between enrolment and 36 months of age in the HDSS areas of Nouna in Burkina Faso and the Bandim Health Project in Guinea-Bissau. The main study on the primary outcome mortality did not provide evidence for NSE of early MV on child mortality in both study areas. The authors conclude that, while reduced power may have been a problem, the absence of NSE in this study could likely have been caused by interference with frequent OPV campaigns in the study areas [18]. For detailed information on the study procedures, please refer to the report of the main study results [18]. In the following, results for the secondary outcome hospitalization or mortality in children between enrolment and 36 months of age will be reported. This composite endpoint was defined as over-night hospitalization in Nouna hospital with or without subsequent recovery, or deaths without previous hospitalization. This composite endpoint is of special interest (i) because early MV could primarily affect outcomes less dramatic than death and (ii) because the analysis is far less affected by power issues due to the frequency of hospitalizations in the study area. The reason for combining deaths with hospitalizations into one endpoint was for interpretation: Hospitalization as such is not the outcome of interest because we are interested in the underlying morbidity not the process of staying in hospital. If we exclude (or censor) children that died before being hospitalized, we may bias our results because the sickest children are excluded (those who died before reaching the hospital).

2.3. Enrolment and randomization

All healthy children who were less than 215 days old and who had received the third dose of Penta at least 28 days prior to enrolment were eligible for this study. Field workers identified eligible children during their monthly visits and invited the mothers one day in advance to bring their children to the vaccination site. At the day of enrolment, informed consent was sought from the mother of the child in the presence of an independent witness and the enrolment form was filled in. Block randomization stratified by sex was used to make sure that sex was balanced between intervention and control group. If the child was assigned to the control group, the mother was given a participant card and told that she would be called for the regular measles vaccination when the child had reached nine months of age. If the child was assigned to the intervention group, the child was immediately vaccinated with one standard dose of Edmonston-Zagreb measles vaccine. Otherwise, the procedures were identical with the children assigned to the control group. The mean age at the second dose of MV was 290 days with standard deviation 17 days in the control group and 291 days with standard deviation 18 days in the intervention group, 106 and 113 children did not receive the second dose of MV before age 18 months, respectively.

2.4. Follow-up

Study enrolment started in May 2013 and ended in August 2015. The last date of follow-up was January 31, 2016, so children enrolled last were followed up for about 5 months, while the children enrolled in the beginning could be followed-up until they reached 36 months of age (for further details, please refer to [18]). At age 9 months, study children in both the intervention and the control group were seen again by the study team for the regular 9 months MV. Children were followed up by the standard HDSS procedures and additional visits of the trial staff, so any deaths and emigrations were recorded. Follow-up of hospitalizations was done by staff of the Nouna hospital. All children enrolled were offered free treatment in Nouna hospital in case of illness. To receive free treatment, mothers had to show the participant card for their children at the time of consultation. The participant IDs of these children were captured at the hospital, together with the date of hospitalization, length of stay, diagnosis, and health status at hospital discharge.

2.5. Changes in context

From October 2014 onwards, a routine second dose of MV at 15 months of age was introduced in addition to the routine dose at age 9 months and a measles and rubella vaccination campaign took place in November 2014, targeting all children between 9 months and 14 years of age. This reduced the observation time of children for the per protocol analyses considerably (Fig. 1). Apart from these major changes in the vaccination schedule, several OPV campaigns took place during the study period, about four campaigns per year, targeting all children under the age of five years. Moreover, there was the introduction of pneumococcal and rotavirus vaccine to the routine child vaccination scheme in Burkina Faso in November 2013, which were added at the time of Penta vaccination.

2.6. Statistical analysis

The outcome used for analysis was the composite endpoint over-night hospitalization in Nouna hospital with or without subsequent recovery, or death without previous hospitalization. Cox proportional hazards regression models were applied with time since study enrolment as underlying time-scale. In a first model, only the first episode of hospitalization or death was considered as event. The second, main model was a recurrent events model, applying the Prentice-Williams-Peterson (PWP) approach [19]. Using the PWP approach multiple periods of observation can be considered within one individual, while the analysis is stratified by the number of previous events. Robust sandwich estimates were used to take account of dependent observations due to observing multiple episodes within one individual [20]. For the

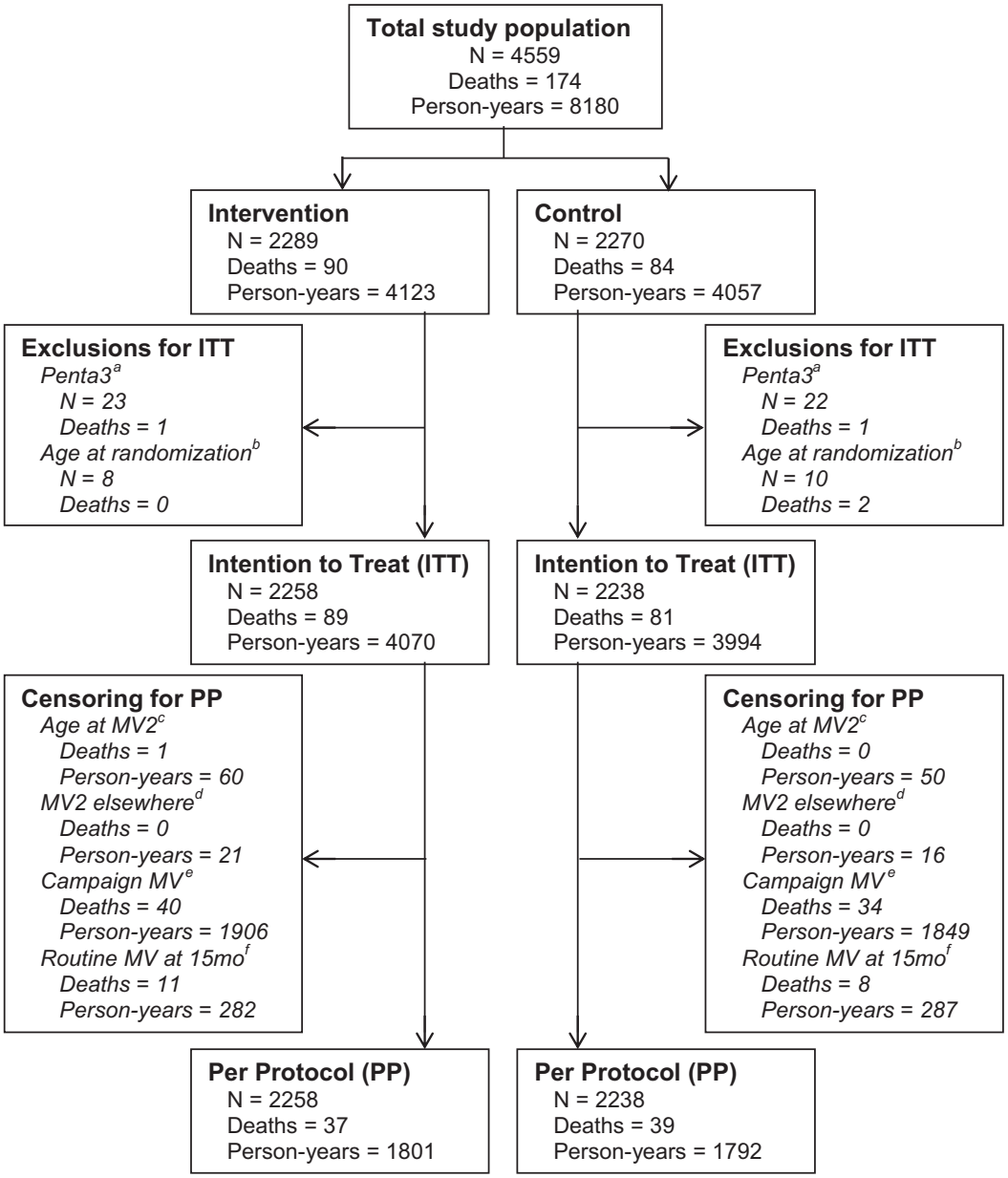

Fig. 1. Flowchart indicating exclusions and censoring. a – Pentavalent vaccine not received or received less than 28 days prior to study inclusion, b – age at randomization younger than 121 days or older than 215 days, c – age at second dose of MV given by study staff older than 18 months, d – second dose of MV received elsewhere, e – eligible for campaign MV (campaign in November 2014), f – eligible for the new standard dose of MV from age 15 months.

intention to treat (ITT) analysis, surviving, non-hospitalized children were censored at age 36 months, at the end of the study (January 31, 2016), or at the time of emigration. The protocol defined the per-protocol analysis as the primary outcome. For the per protocol (PP) analysis, children were additionally censored at the age of 18 months (if they had not received the 9 months dose of measles vaccine), at the time of knowing that they had received the 9 months MV elsewhere, at the time of the measles campaign if the child was already 9 months old, or at age 15 months if that age was reached after October 01, 2014, or at October 01, 2014, if they were older than 15 months, to make sure that the MV status was known for all children in the analysis. All analyses were adjusted for age at enrolment and stratified by sex.

To investigate possible differential effects by sex, two different models were calculated for boys and for girls, based on the per-protocol population. Additionally, an interaction term between intervention and sex was added to the main model. The effect of the early MV might also differ between the interval before the 9 months vaccination (Interval 1: one MV in the intervention group and zero MV in the control group) and after the 9 months vaccination (Interval 2: two MV in the intervention group and one MV in the control group), so two different models were calculated, both based on the per-protocol population.

2.7. Sensitivity analysis

For the purpose of sensitivity, we applied different models with the following modifications: (i): age of the children was used as underlying time-scale, (ii) the model was adjusted for OPV campaigns as a time-dependent variable and we calculated the effect of the intervention in the group that had not (yet) been exposed to any OPV campaign since enrolment, (iii) we analyzed the effects of early MV before rotavirus vaccine was introduced by excluding children that were eligible to receive rota virus vaccine prior to enrolment, and (iv) only hospitalizations were considered as endpoint, while deaths were censored. All analyses were performed with SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

2.8. Ethical considerations

The trial protocol was approved by the relevant ethical committees in Guinea-Bissau (Comité Nacional de Ética na Saúde), Burkina Faso (Le Comité d'Ethique pour la Recherche en Santé, Comité technique d'autorisation d'essais cliniques and le Comité Institutionnel d'Éthique de Nouna), Germany (The Ethical Committee of the University of Heidelberg) and Denmark (Consultative approval by the Danish Central Ethical Committee). Due to changes in national vaccination policies during the course of the study, protocol modifications with respect to sample size were submitted and approved by the ethical committees. The data safety and ethics monitoring board (DSEMB) approved the suggested changes before submission and approved the analysis plan before data lock.

3. Results

We randomized a total of 4559 children, 2289 to the intervention and 2270 to the control group (Fig. 1). Of these, 63 children did not fulfil the enrolment criteria because they were either older than 215 days or had not received the third dose of Penta at least 28 days before enrolment. This led to a final number of 2258 children in the intervention and 2238 children in the control group. In the ITT analysis, the child mortality rate between age 4.5 months and 36 months in the study population was 21.1 deaths per 1000 child-years, based on 170 deaths. The per-protocol analysis had only 76 deaths and 45% of the person-time and though the children were younger. The mortality rate was similar in the PP (21.2 per 1000 child-years) and the ITT analyses. The majority of children were censored because of the MV campaign or the introduction of the routine second dose of MV at age 15 months.

Within the PP population, we observed 404 hospitalization episodes and 76 deaths of which 60 occurred outside hospital, summing up to 464 events (Table 1). The majority of children were hospitalized with a diagnosis of malaria (94%), and malaria/acute febrile illness was also the most frequent diagnosis for deaths without previous hospitalizations (Supplementary Table 1). None of the admissions or deaths were due to measles infection. The number of hospitalizations was similar between intervention and control group, with 216 first episodes in the intervention and 207 first episodes in the control group (Table 2, Supplementary Fig. 1).

There was no difference in hospitalization or mortality between intervention and control group in the main regression model with the PWP approach (HR = 1.00, 95% CI 0.83–1.20) (Table 2). The same was true in analyses that were stratified by sex and by time before/after the 9 months vaccination (Table 3) and there was no significant interaction effect between intervention and sex. The analysis using the ITT population was based on a larger number of hospitalization and mortality episodes (805 events) but yielded a similar result (HR 1.05, 95%CI 0.92–1.21) (Table 2).

3.1. Sensitivity analysis

Using age of the children as underlying time-scale (i) had no effect on the results from the main analysis (data not shown). Due to the frequent OPV campaigns, all children included in the study had possibly received OPV via an OPV campaign before study enrolment. Campaigns with OPV appeared to have a beneficial effect, since the risk of hospitalization or death was 36% (95% CI 6–56%) lower after an OPV campaign as compared to before an OPV campaign (ii) (Supplementary Table 2). Interaction effects were not apparent between the intervention and OPV campaigns (p-value for interaction 0.3). There was a beneficial effect of the early MV in children that had not yet been eligible for campaign OPV since study enrolment (HR = 0.84, 95% CI 0.55–1.29), but this was a non-significant result based on a small sample of 85 events and 684 child-years (Supplementary Table 3). When the effect of early MV was studied in children enrolled before the introduction of the rotavirus vaccine only (iii), the hazard ratio was rather higher than in the total sample but this was far from significant (HR = 1.10, 95% CI 0.87–1.41). In sensitivity analyses, in which deaths without previous hospitalizations were censored (iv), results did not differ from the main results (HR = 1.02, 95%CI 0.84–1.24) (data not shown).

4. Discussion

In this study, we did not find any effect of an early dose of MV on subsequent hospitalization or mortality. This was true for the period before the 9 months vaccination, when children in the control group were unvaccinated against measles, and after the 9 months vaccination, when the intervention group had received two doses of MV and the control group had received one dose of MV. The absence of beneficial NSEs of early MV on hospitalizations in the present study is in line with the main study findings on child mortality [18].

Previous research from Guinea-Bissau, which studied the effect of an early dose of MV on hospitalizations in a RCT, found that there were significantly less hospitalizations in the intervention as compared to the control group [13,21]. A sub-study in a different RCT in an urban area of Guinea-Bissau found that parents of

Table 1
Events according to per protocol and ITT analysis.

Time interval	N	Hospitalizations			Deaths outside hospital	Total number of events	Person-years
		With discharge	Death before discharge	Withdrawn before discharge			
Per protocol analysis							
Before first hospitalization	4496	350	15	3	55	423	3434.4
After first hospitalization	350	31	1	0	4	36	145.5
After second hospitalization	31	4	0	0	1	5	10.2
After third hospitalization	4	0	0	0	0	0	0.8
Total	4496	385	16	3	60	464	3590.9[a]
ITT analysis							
Before first hospitalization	4496	540	24	2	118	684	7400.0
After first hospitalization	539	79	2	0	22	103	587.0
After second hospitalization	79	14	0	0	4	18	61.1
After third hospitalization	14	0	0	0	0	0	11.6
Total	4496	633	26	2	144	805	8059.8

[a] The number of person-years is slightly lower than in Fig. 1 because the time in hospital was not considered under risk.

Table 2
Intervention effect on hospitalization or mortality in Cox regression according to per protocol and ITT analysis.

Model	Group	N	Event	Person-years	Rate	Hazard ratio	95% Confidence Interval	p-value
Per protocol analysis								
First episode only	Control	(2238)	207	1717	120.6	1		
	Intervention	(2258)	216	1717	125.8	1.04	0.86–1.26	0.66
All episodes (PWP[a])	Control	(2238)	231	1791	129.0	1		
	Intervention	(2258)	233	1800	129.5	1.00	0.83–1.20	1.00
ITT analysis								
First episode only	Control	(2238)	328	3680	89.1	1		
	Intervention	(2258)	356	3720	95.7	1.07	0.92–1.24	0.38
All episodes (PWP[a])	Control	(2238)	387	3992	96.9	1		
	Intervention	(2258)	418	4068	102.8	1.05	0.92–1.21	0.46

All models adjusted for age at enrolment and stratified by sex.
[a] PWP – Prentice-Williams-Peterson approach for recurrent events.

Table 3
Stratified intervention effect on hospitalization or mortality in Cox regression according to the per protocol analysis.

Stratum	Group	N	Event	Person-years	Rate	Hazard ratio	95% Confidence Interval	p-value
Before 9 months vaccination[a]	Control	(2238)	77	747.5	103.0	1		
	Intervention	(2258)	81	756.0	107.1	1.06	0.77–1.45	0.73
After 9 months vaccination[a]	Control	(2018)	154	1043.7	147.6	1		
	Intervention	(2021)	152	1043.8	145.6	1.01	0.80–1.27	0.94
Boys	Control	(1122)	133	897.9	148.1	1		
	Intervention	(1126)	118	894.9	131.9	0.88	0.69–1.13	0.32
Girls	Control	(1116)	98	893.3	109.7	1		
	Intervention	(1132)	115	904.9	127.1	1.16	0.88–1.53	0.29

All models adjusted for age at enrolment, PWP- Prentice-Williams-Peterson approach used for recurrent events.
[a] Stratified by sex.

children randomized to early MV were less likely to report episodes of fever, vomiting, and diarrhea, than parents of children in the control group [15]. Skin reactions were also less frequently observed by the study staff in the children in the intervention than in the control group. Four studies from Denmark, the Netherlands, Italy, and the US have provided evidence that children were less likely to be hospitalized, particularly for respiratory infections if their last vaccination was the measles-mumps-rubella vaccine than if their most recent vaccination was DTP with polio and haemophilus influenza type b vaccine [14,22–26]. Though some of the effect may have been related to healthy vaccinee bias [22], the beneficial effect on respiratory infections was systematic for measles-mumps-rubella (MMR) compared with DTP-containing vaccine [14,23,25,26]. In the present study, the main diagnosis for about 95% of hospitalizations was malaria, which is likely to be an overestimation [27] but prohibited studying the effect of early MV on cause-specific hospitalizations. In previous studies on early MV and cause-specific hospitalizations, similar protective NSE were found for the two main diagnostic groups malaria and respiratory infections [13,21].

Recent research has investigated possible NSEs of OPV, which has been administered in frequent campaigns in the study area with the aim to eradicate polio. The addition of OPV to the BCG vaccination at birth was significantly associated with lower mortality as compared to BCG vaccination only in an RCT in Guinea-Bissau [5]. Two observational studies from Guinea-Bissau suggest beneficial NSEs of OPV campaigns on child mortality, and provide estimates of a 20–25% reduction after the OPV campaigns as compared to before the OPV campaigns [6,7]. The frequency of OPV campaigns was very high in our study area with about four OPV campaigns each year during the study period. It is thus possible that the NSEs of the OPV campaigns, which almost all study

children were exposed to, obscured any NSEs of the early dose of MV. In a sensitivity analysis, in which we studied children only until they were eligible for their first OPV campaign after enrolment, we only found a small and non-significant benefit of the early MV. However, this could be caused by the very low number of child-years observed prior to the OPV campaigns and due to the OPV campaigns conducted between birth and enrolment, which reached all children in study population. In the first RCT of early MV from Guinea-Bissau, a beneficial effect of early MV was mainly found for children who had not received campaign OPV before enrolment and, as in the present trial, there was only a slight beneficial effect for children who had received campaign OPV before enrolment but no campaign OPV after enrolment [7]. Furthermore, Do et al., in their study of reported disease symptoms, also stratified their analysis into before and after OPV campaigns [15]. They found that the effect of early MV on reported vomiting and diarrhea were stronger before the OPV campaigns than after the OPV campaigns. The recently introduced rotavirus vaccine is also a live attenuated vaccine and could thus have influenced the study results similarly, even though NSEs of rotavirus vaccine have not been looked at to date. However, in a sensitivity analysis, the expected beneficial effect of the early MV was even less apparent in the early randomized subsample that had not yet received rotavirus vaccine as part of the vaccination schedule. This indicates that inclusion of rotavirus vaccine into the vaccination schedule did most likely not affect our results. Besides possible NSEs, the introduction of the rotavirus and the pneumococcal vaccine may also have contributed to the strong decrease in mortality that was observed in the study area during the conduct of the trial by preventing deaths from diarrhea of pneumonia.

The trial was initially set up with EU funding to study the effect of an early MV in a setting, in which the children receive only the recommended vaccinations according to the WHO schedule. It is thus a limitation of our study that this was not possible due to the numerous campaigns and changes in age of vaccination. Frequent OPV campaigns are likely to have obscured any beneficial effect of early MV. In addition, the total observation time for the per-protocol analysis was much lower than planned because of the MV campaign and the introduction of the 15 months MV in 2014. However, there was sufficient power (80%) to detect a decrease of 23% in hospitalization or mortality in the per-protocol analysis, as the study was initially powered to detect a significant difference in mortality, an outcome which is much less frequent than hospitalizations. Although the study ID did not reveal the group allocation of the children and so study staff and the hospital staff were uninformed about the MV status of the children, mothers were aware of the group allocation of their children and could thus have informed the hospital staff about the MV status of their children. However, the proportion of children who died during admission did not differ by group, consistent with no differential threshold for admission by group. Nor was there any indication that fever, a known adverse effects of MV, caused admissions. Only six hospitalizations were recorded within the first 14 days after enrolment and these were evenly distributed between intervention and control group. It is also unlikely that MV status influenced the care-seeking behaviour of the mothers, as measles infection has become very rare in the study area, so the perceived health risk for children should have been the same in the intervention and control group.

5. Conclusion

This study does not provide evidence for an effect of early MV on child hospitalization or mortality. This could possibly be explained by the unforeseen frequent OPV campaigns in the study area, as the NSEs of OPV might have strongly affected both children in the intervention and control group. More research is needed on the NSE of childhood vaccines to clarify the different findings from existing studies on this subject.

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Conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.02.104.

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